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#19

Patent Docket P1780P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Group Art Unit: 1642
Kathy L. Miller et al.	Examiner: Misook Yu
Serial No.: 09/813,341	Confirmation No: 1230
Filed: March 20, 2001	Customer No: 09157
Title: Multivalent Antibodies and Uses Therefor	
	EXPRESS MAIL LABEL NO.: EV 351 926 794 US
	DATE OF DEPOSIT: SEPTEMBER 26, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

DECLARATION UNDER 37 CFR §1.131

Sir:

We, Kathy L. Miller and Leonard G. Presta, do hereby declare and say as follows:

1. We are inventors of the subject matter of the above-identified patent application. All work described hereinafter was performed by us or on our behalf in the Unites States of America.

2. Prior to July 14, 1999, we conceived of and reduced to practice an isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region.

3. Evidence of the reduction to practice of the claimed invention is set forth in the exhibits attached to this declaration which represent excerpts from our laboratory notebooks with dates obscured.

4. Exhibit A provides four laboratory notebook entries, pages 9, 10, 11 and 43, by Kathy L. Miller. A diagram of a vector for tetravalent antibody 4H6oct is shown on page 9, in which vector the two Fabs in tandem ~~arms~~ of each polypeptide (boxes 1 and 2) are cloned amino-terminal to an Fc region. Expression of this vector and purification of the resultant protein (page 10) yielded the 4H6oct antibody (page 11). Also shown on notebook page 11 is a gel isolation of tetravalent antibody OctHer2. Expression of a similar vector, but having 4H6 (arm 1) and 16E2 (arm 2) cloned amino-terminal to an Fc region yielded the tetravalent 4H6/16E2oct antibody shown on notebook page 43. The terms 4H6 and 16E2 refer to the DR4 and DR5 antigen binding regions, respectively, as shown on notebook page 43. The experimental work in Exhibit A was completed prior to July 14, 1999.

9/24/03
KM 09-26-03

We declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 09-26-03 Kathy L. Miller

Kathy L. Miller

Date: Sept. 26, 2003 Leonard G. Presta

Leonard G. Presta

Exhibit A

Project No.

TITLE Book No. 31884 9

From Page No. 6

SET-UP PCR RXN TO SEQUENCE 4H6OCT CORRECTED BY MOT. VIA ABI (ALSO SEQU. >EF36 BOOK 31885 p.7)

PCR RXN		PGEM CNTL
BIG DYE RXN	8 µl	8 µl
TEMPLATE (500ng)		2 µl
PRIMER (NEAT)	1 µl	4 µl
DMSO	1 µl	1 µl
H_2O		5 µl
	20 µl	20 µl

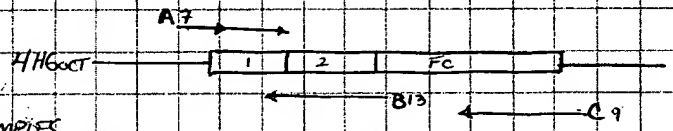
4H6OCT = MUT

9-9#7
9-16#1
9-16#3

PRIMERS: A = KMSEQ 7
B = spigg 13L
C = spigg 9A

4H6OCT-MUT	ng/µl	DILUTION	≈500ng	H_2O
9-9#7	2317	1:3	1 µl	9 µl
9-16#3	903	1:2	1 µl	9 µl
9-16#1	2397	1:3	1 µl	9 µl

LANE# ON GEL	
21	9-7A
22	9-7B
23	9-7C
24	16-3A
25	16-3B
26	16-3C
27	16-1A
28	16-1B
29	16-1C



[redacted] PROCESS SAMPLES

1) 250 µl 826-50 SEPHAROSE/MINI COLUMN (IN MICROTUBE)
2) SPIN 2' 3rpm. PLACE COLUMN IN FRESH MICROTUBE
3) ADD SAMPLE W/OUT DISTURBING BED. SPIN 2.5' 3rpm
4) DRY BY LYOPHILIZATION ≈ 30'
5) RESUSPEND IN 6 µl LOADING DYE
6) INCUBATE 95°C 2'; ON ICE
7) LOAD 2 µl

PAUSE; LOAD ODDS#; RUN INTO GEL PAUSE; CLEAN WELLS, LOAD EVEN#S, RUN TERMINATE

WHEN PRESS RUN, ASKS TO "SAVE AS: GELFILE-DATE

To Page No.

Witnessed & Understood by me,	Date	Invented by [redacted] Recorded by	Date [redacted]

Project No. [redacted]

Book No. 31884 TITLE Exhibit A (continued)

From Page No. 8

CONCENTRATE & PURIFY OCTOPUS PROTEIN CONSTRUCTS

1) COLLECT SUPS FROM TRANSFECTED CELLS INTO 250ml CONICAL FLASK, CENTRIFUGE 2500rpm 5' 4°C

2) TRANSFER SUPS TO T75 FLASK. PER 50ml ADD: 500µl 0.1M PMSF (0.001M)
500µl 5mM AEBSF 119mg PMSF/ml APROTININ (

9 x 25 = 225ml
4.5 x 500 = 2.25ml PMSF
x50 = 225µl APROTININ

3) CONCENTRATE USING SPIN-FILTER CONC WITH YM100 DIAFILTERS; CONC TO 10-15ml STARTING VOL

4) WASH PROTEIN A COLUMN (0.5ml BED VOL) WITH 10ml 1x BINDING BUFFER

5) ADD SAMPLE TO COLUMN

6) WASH COLUMN W/10ml 1X BINDING BUFFER

7) ELUTE W/ 2.5ml ELUTION BUFFER INTO TUBE CONTAINING 500µl COLD 1M TRIS, PH 8.0, TO NEUTRALIZE THE ACID ELUTION

8) CONCENTRATE TO ≈1ml IN PBS USING CENTRIPREP-30 (CONC + BUFF XCHANGE W/ 2x15ml PBS)

9) FILTER W/ MILLEX GV 0.22µm FILTER

	OD 280	1:10 DILUTION	EXT. COEFF 1.38 (OTHER 2)
OTHER 2	0.502	3.6 mg/ml	$\frac{(OD\ 280)(10)}{1.38} = mg/ml$
4/16 OCT 9-9-7	0.005		
* → 9-16-1	0.098	0.7 mg/ml	
9-16-3	0.012		

To Page No. ____

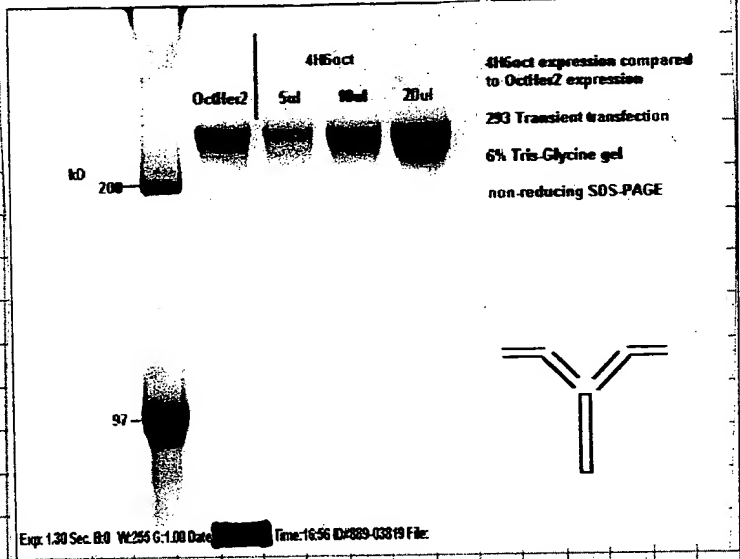
Witnessed & Understood by me,	Date	Invented by Patty Mill	Date [redacted]
		Recorded by	

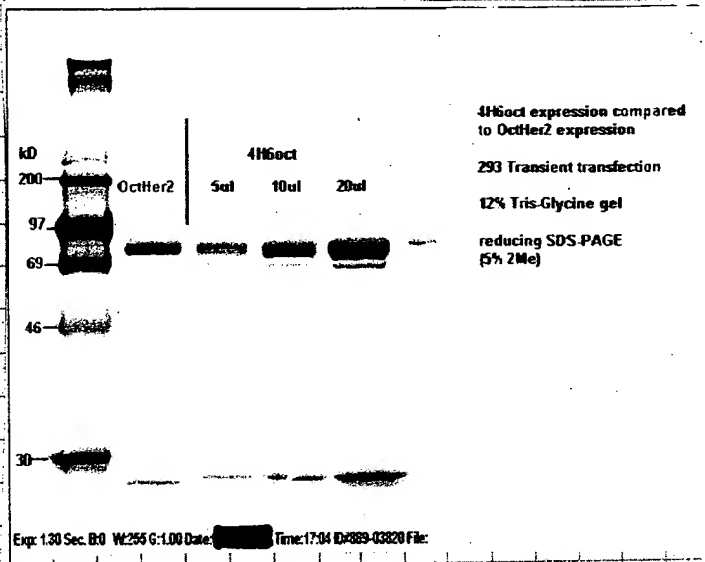
From Page No.

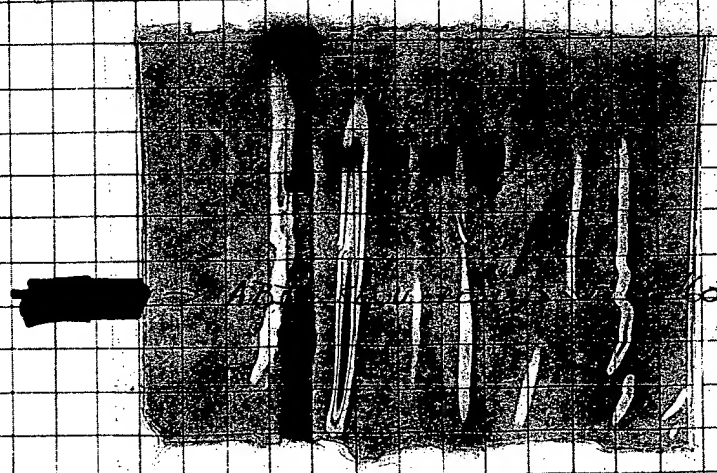
COOMASIE STAIN OF SDS-PAGE. DECIDED TO LOOK AT 4H6OCT 9-16-1 → HIGHEST CONC.

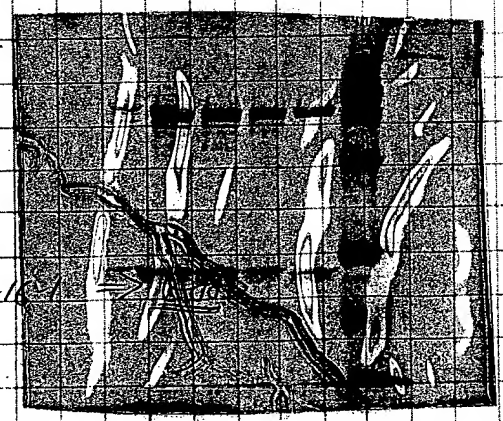
14% TRIS-GLYCINE ⊕2ME REDUCING
6% TRIS-GLYCINE ⊖2ME NONREDUCING

BOIL SAMPLES 5'; QUICK-SPIN; LOAD; RUN ~40mAMPS ON ICE
STAIN 2HRS
DESTAIN O.N.









To Page No.

Witnessed & Understood by me,	Date	Invented by [redacted]	Date [redacted]
		Recorded by	

Exhibit A Continued

Project No.

TITLE

Book No. 31884

From Page No. 40

CONCENTRATE & PURIFY 4H6/16E2 OCT PROTEIN FROM 293 TRANSFECTIONS ; YM100 FILTER

SEE PG. 38 FOR PROTOCOL

PURIFY OVER PROTEIN A STEP.

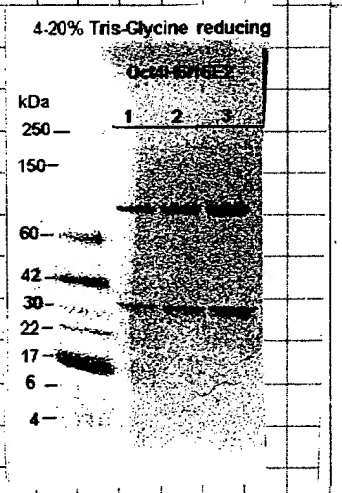
OD 280 1:10 → 800ml VOLUME

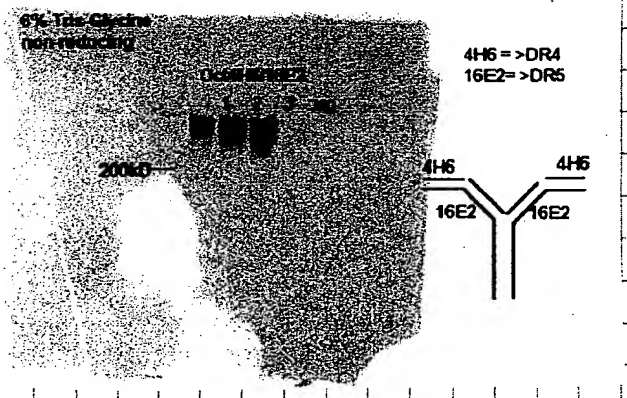
0.139

$$\frac{(0.139)(10)}{1.38\ (\text{EXT COEFF})} = 2.0\ \text{mg/ml}$$

(10 = DILUTION FACTOR)

[redacted]





To Page No.

Witnessed & Understood by me,	Date	Invented by Kathy Mill Recorded by	Date [redacted]

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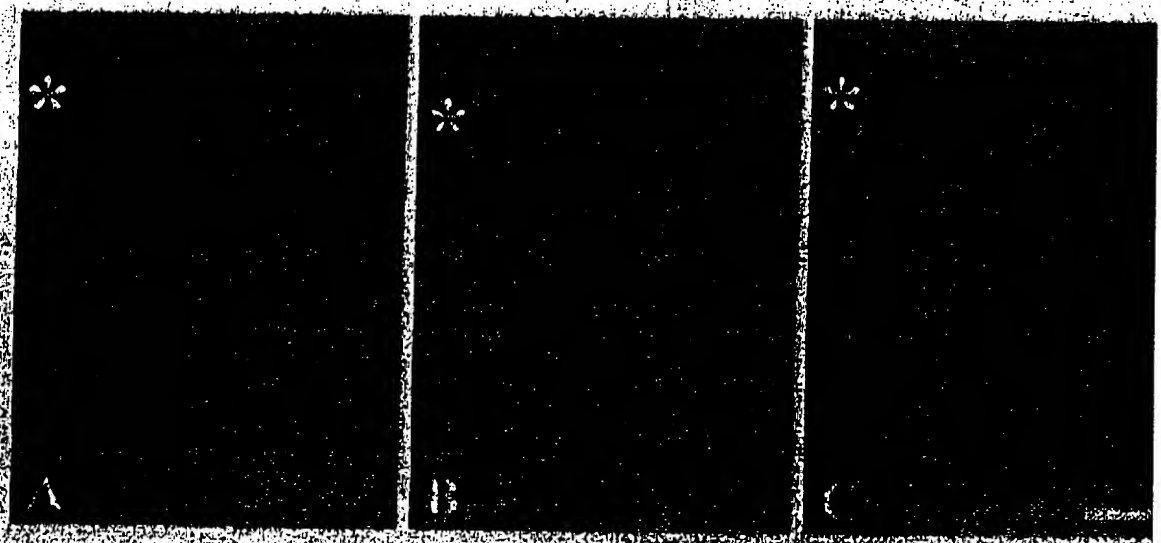

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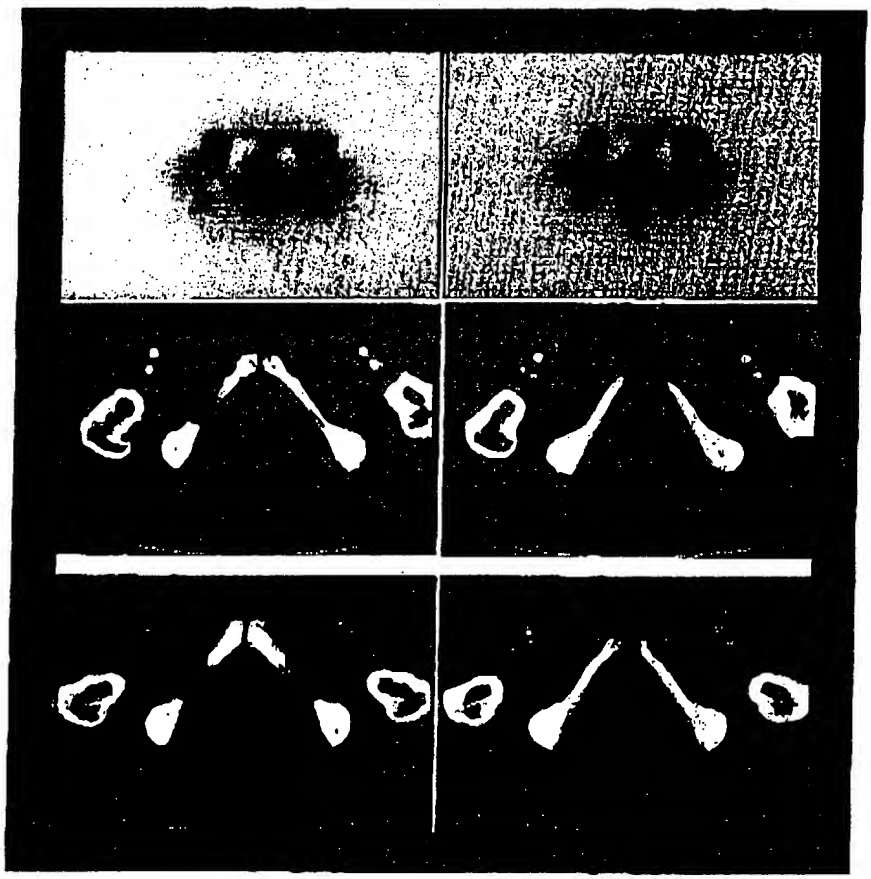

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October 15-17, 1998

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